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09/838,718	04/19/2001	Lothar Steidler	4779US	3041

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/838,718	Applicant(s) STEIDLER ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-12,14-18,21-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3,4,6-12 and 14-17* is/are allowed.

6)☒ Claim(s) *18 and 21-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Final Rejection

Claims 1, 3, 4, 6-12, 14-18, 21-36 are pending examination.

Applicants' traversal, the amendment to claims 1 and 21, the addition of claims 22-36 in paper no. 18 filed on 7/7/03 is acknowledged and considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 remains and claims 18 and 22-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preventing the onset of colitis in a IL10-/- mouse, said method comprising administering a medicament comprising an amount of a cytokine- or cytokine antagonist-producing genetically modified, non-invasive Gram-positive bacteria, wherein the administration of said medicament results in prevention of intestinal mucosal inflammation, and wherein said, does not reasonably provide enablement for a method of preventing IBD in a mammal using the claimed method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed method of the instant application embrace a method of preventing inflammatory bowel disease (IBD) in a mammal by administering a cytokine or cytokine-antagonist producing genetically modified Gram positive bacterial strain to the mammal.

The art of record teaches that the etiology of IBD remains poorly understood and several genetic and environmental factors have been implicated in the pathogenesis of IBD (Papadakis et al. Annu. Rev. Med., Vol. 51, pp.289-298, 2000). The art of record further teaches IBD can be separated into ulcerative colitis (UC) and Crohn's Disease (CD) and that some animal models have some features of CD and UC, although no model has actually mirrors the changes as seen in humans (Leach et al., Toxicologic Pathology, Vol. 27, page 125, 1999).

Furthermore with respect to the animal model (IL10 deficient mice) used in the examples set forth in the disclosure, the state of the art as exemplified by Leach teaches that the role of genetic influences on colitis can potentially be evaluated in IL10 -/- mice (page 127). Leach also teaches that when administering exogenous IL10 was initiated after disease was established at 3 months of age, colitis was ameliorated but not prevented (page 128). It appears from the art of record that IL10 is one factor involved in IBD and in view of the complex nature of IBD, it is not apparent to one skilled in the art how reducing inflammation in IL10 -/- mice reasonably correlates to the method embrace in the claims.

The specification further supports the art of record by stating that, "the cause of IBD is unknown...The pathogenesis of CD and UC probably involves interaction between genetic and environmental factors although no definite etiological agent has been identified so far" (page 4). Thus, the state of the art for preventing IBD in a mammal was considered unpredictable.

The as-filed specification contemplates a cytokine-producing Gram-positive bacterial strain can be used for the preparation of a medicament to treat inflammatory bowel disease. More specifically, the specification specifically teaches a recombinant Lactococcus lactis (L. lactis) comprising a gene encoding an IL-10 protein. The recombinant bacteria are then injected into the peritoneum of healthy mice or mice with induced colitis. The pathology of chronic colitis is characterized by a decrease in colon length and epithelial damage and infiltration of lymphocytes. Example 2, mice are euthanized and a histological score of the colon demonstrates an increase in colon length of the mice with induced colitis after the treatment with the recombinant IL producing L. lactis compared to mice with induced colitis and untreated and control mice. The specification also demonstrates the prevention of the onset of colitis in IL10-/- mice by intra-gastric inoculation with IL-10 producing L. lactis and 50% reduction of chronic colitis induced by DSS in mice (Example 5, pages 17-18 and Figure 10).

The specification provides sufficient guidance for one skilled in the art to practice a method of preventing the onset of colitis in a IL10-/- mouse using cytokine-or cytokine antagonist producing genetically modified, non-invasive Gram-positive bacteria. However, in view of the In Re Wands Factors, the as-filed specification is not enabled for the full scope of the claimed method. The specification teaches how to prevent onset of colitis in IL10-/- mice using the claimed Gram-positive bacteria. The specification does not provide sufficient guidance for how to reasonably extrapolate from preventing colitis in IL10-/- mice to preventing IBD in a genus of mammals using the claimed methods. The art of record teaches that animal models of intestinal inflammation have opened new avenues for the development and testing of novel therapeutics (Papadakis et al., Annu. Rev. Med., Vol. 51, pages 289-298, 2000, page 289).

However, the art of record is absent for teaching how to prevent IBD in a mammal using any type of IBD therapy. In addition, IBD can be separated into ulcerative colitis (UC) and Crohn's Disease (CD) and that some animal models have some features of CD and UC, although no model has actually mirrors the changes as seen in humans (Leach et al., Toxicologic Pathology, Vol. 27, page 125, 1999). In view of the art of record, the as-filed specification does not provide sufficient guidance for one skilled in the art to reasonably correlate from the features observed with colitis to the features of IBD or Crohn's Disease. The as-filed specification does not provide sufficient guidance or factual evidence to reasonably extrapolate from preventing colitis in experimental mice to preventing IBD in a mammal. Thus, one skilled in the art would not be enabled to practice the full scope of the claimed embodiment.

Furthermore, with respect to claim 25, the specification does not teach one skilled in the art how to practice the claimed method. The claimed method embraces preventing Crohn's Disease and ulcerative colitis (UC) in mammal at the same time or at different time points in a mammal's life. The specification and the art or record do not teach that a mammal can have Crohn's Disease and ulcerative colitis at the same time. In addition, the specification does not teach how to prevent both diseases at the same time or at different time points in a mammal's life span. The art of record further teaches IBD can be separated into UC and Crohn's Disease (CD). The specification does not teach one skilled in the art how to determine if a mammal is susceptible to both diseases at the same time. Thus, the claimed method is not considered enabled.

Thus, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the specification to the full scope of the claimed method. Even if a

protective response has been shown in IL10-/- mice, it is not apparent as to how the mouse model is reasonably extrapolated to the full breadth of the claimed invention, encompassing any mammal particularly given that there is no evidence showing that the mice model is a general phenomenon, and given the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made provide sufficient guidance and/or evidence to reasonable enable the claimed method for preventing colitis in an IL-10-/- mouse and not the full scope of the claimed method. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the application's disclosure, the unpredictability of preventing IBD in a mammal and developing effective therapies for preventing IBD in a mammal. In addition, the presence of a working example as provided in the as-filed specification do not reasonably extrapolate to the claimed invention, particularly given that there is no evidence that preventing the onset of colitis in IL10-/- mice can be reasonably extrapolated to preventing IBD in a mammal.

Applicant's arguments filed 7/7/03 have been fully considered but they are not persuasive because in view of the In Re Wands Factors, the as-filed specification does not teach one skilled in the art how to practice the full scope of the claimed invention.

With respect to the argument that based on genetic profile, subjects that have a substantially increased risk of developing IBD can be identified and IBD in these subjects can be prevented using the claimed method (See pages 10-11). The argument is not found persuasive because the specification and art of record at the time the application was filed **(10/20/98)** do not teach one skilled in the art how to determine what subjects will have IBD. The specification

states, "the cause of IBD is unknown...The pathogenesis of CD and UC probably involves interaction between genetic and environmental factors although no definite etiological agent has been identified so far" (page 4). Thus, it would take an undue amount of experimentation for one skilled in the art to practice the full breadth of the claimed invention.

Furthermore, with respect to the argument that in view of the post-filing articles that teach genetic markers for IBD and other markers identified in the future, subjects can easily be tested for currently known genetic markers for IBD (see page 10). The argument is not found persuasive, because at the time of filing (**10/20/98**), the art of record teaches that the etiology of IBD remains poorly understood and several genetic and environmental factors have been implicated in the pathogenesis of IBD (Papadakis et al. Annu. Rev. Med., Vol. 51, pp.289-298, 2000). The art of record further teaches IBD can be separated into ulcerative colitis (UC) and Crohn's Disease (CD) and that some animal models have some features of CD and UC, although no model has actually mirrors the changes as seen in humans (Leach et al., Toxicologic Pathology, Vol. 27, page 125, 1999). The as-filed specification does not provide sufficient guidance and/or factual evidence to led one skilled in the art to use the genetic markers for IBD taught in the post-filing articles. See In re Wright, 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

With respect to argument that preventing the onset of IL-10 deficient mice using the claimed methods would lead one of skilled in the art to preventing IBD in people with genetic predisposition for the development of IBD using the claimed method. The argument is not found persuasive because while it is acknowledged that the art of record and the specification teach that the onset for colitis in IL-10 mice is known (3-8 weeks after birth). The as-filed specification

and the art of record are absent for teaching when the onset of IBD in any other mammal. Thus, it would take an undue amount of experimentation for one skilled in the art to practice the full breadth of the claimed invention.

With respect to the argument the statement ("This approach **may** lead to better methods for cost-effective and long-term management of IBD in humans.") and the statement such as this undoubtedly would not be published in a renowned peer-reviewed article like *Science* if the extrapolation from mice to other mammals was unacceptable to those of skill in the art (page 11). The argument is not found persuasive because in view of the In Re Wands Factors, the as-filed specification does not teach one skilled in the art how to practice the full scope of the claimed invention.

With respect to the argument that, "Professor Blumberg has invited the applicants to began clinical trials based on the data published in the journal *Science*" and "preliminary results are reportedly very encouraging" (page 12). The argument is not found persuasive because the statements do not led one skilled in the art that the specification was enabled for preventing IBD or ulcerative colitis and/or Crohn's Disease in a mammal using the claimed method.

In addition, in response to applicant's argument that, "preliminary results are reportedly very encouraging". The argument is not found persuasive because MPEP § 716.01(c) states:

> The arguments of counsel cannot take the place of evidence in the record. In re Schulze,346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the

date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

With respect to the argument that, "the results set forth in the specification illustrate that administration of the medicament may both reduce inflammation in those areas of the intestine already affected and prevent inflammation in other portions of the intestine, i.e., prevent spread of the inflammation." (see page 12). The argument is not found persuasive because the specification does not define the term "prevention" and does not define the term as preventing spread of the inflammation. The art of record defines the term "prevention" as to keep from happening or existing (see Merriam-Webster's Collegiate Dictionary, Tenth Edition, Springfield, Massachusetts, USA, 2001, page 922.). In view of the definition of the term "prevention" set forth by the art of record and the In Re Wands Factors, the as-filed specification does not teach how to prevent IBD or how to prevent ulcerative colitis and/or Crohn's Disease in a mammal using the claimed method.

Furthermore, the Declaration by Professor Lothar Steidler under 37 CFR 1.132 filed on 1/30/03 is insufficient to overcome the rejection of claims 21-36 based upon 112 first paragraph rejection as set forth in the instant Office action because of the same reasons as set forth in the last office action (see paper no. 16, filed 3/31/03).

Applicant's arguments, see paper no. 18, filed 7/7/03, with respect to 112 second paragraph rejection have been fully considered and are persuasive. The rejection of claims 1, 3, 4, 6-12, 14-18 and 21 has been withdrawn because of the amendment to the claims.

Conclusion

Claims 1, 3, 4, 6-12, and 14-17 are in condition for allowance because the claims are free of the art of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER